UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

09/800,909 03/08/01 WALLACH, D

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/800909	03/08/01	WALLACH, D	

HM12/0925

BRINKS HOFER GILSON & LIONE
PATENT AND TRADEMARK CAUSES
SUITE 3600
524 NINTH STREET, N.W.
WASHINGTON DC 20001-5303

EXAMINER	
ART UNIT	PAPER NUMBER
1644	09/25/01

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 7/2/01

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 (2) month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-16 is/are pending in the application.
Of the above, claim(s) 1-11 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 12-16 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
☑ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.
☑ received in Application No. (Series Code/Serial Number) 08/477347; 08/321685
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

DETAILED ACTION

1. Applicant's election without traverse of Group III (claims 12-16) in Paper No. 4 is acknowledged.

Claims 12-16 are being acted upon presently.

Claims 1-11 have been withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to the nonelected inventions

2. Applicant is invited to verify that the instant claims have written support and enablement under 35 USC 112, first paragraph, for the instant claims to priority U.S. and foreign applications. The instant claims may not have the benefit under 35 U.S.C. § 120 and § 119 of all of the priority filing dates. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph

3. Applicant should amend the first line of the specification to update the status of the priority documents. USSN 08/476,862 is now U.S. Patent No. 6,262,239.

4. Formal drawings have been submitted which comply with 37 CFR 1.84.

Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes (e.g. Figures 2A-B).

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 12-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection

The specification does not provide adequate written description of the claimed invention, for "the natural ligand receptor of the TNF/NGF receptor family", "TBP-II" and "p75 TNF receptor" because the relevant identifying characteristics such as structure or other physical and/or chemical characteristics of said molecules are not set forth in the specification as-filed, commensurate in scope with claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicant is claiming a very broad generic class of molecules encompassing "the natural ligand receptor of the TNF/NGF receptor family", "TBP-II" and "p75 TNF receptor" based upon the support of the disclosure of a limited representative number of species (e.g. SEQ ID NO:2). The instant invention encompasses any "natural ligand receptor of the TNF/NGF receptor family", "TBP-II" and "p75 TNF receptor", yet the instant specification does not provide sufficient written description as to the critical structural features of said "molecules" and the correlation between the chemical structure and the desired structural and/or function.

For example, see Krakauer et al., in Paul (ed.) Fundamental Immunology Fourth Edition, Lippincott-Raven Publishers, Phildelphia, 1999, pages 775-784).

Applicant is relying upon certain structural and/or biological activities and the disclosure of a limited representative number of species to support an entire genus / genuses. The reliance on the disclosed limited examples of a particular member(s) of the "TNF/NGF receptor family", "TBP-II" and "p75 TNF receptor" does not support the written description of any "member" of these "molecules".

It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biological or pharmacological activities. Therefore, structurally unrelated "molecules" encompassed by the claimed invention other than those disclosed in the specification as filed (e.g. SEQ ID NO: 2), would be expected to have greater differences in their structural and functional characteristics and attributes.

Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required

The instant specification and claims do not provide sufficient functional characteristics coupled with a known or disclosed correlation between function and structure. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus / genuses, and because the genus / genuses is / are highly variable, the disclosure of a particular TNF-R for example is insufficient to describe the genus of molecules, encompassed by the claimed invention.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In the absence of structural characteristics that are shared by members of the genus genuses of "the natural ligand receptor of the TNF/NGF receptor family", "TBP-II" and "p75 TNF receptor", one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus / genuses. Thus, applicant was not in possession of the claimed genus / genuses. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

8. Claims 12-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "TNF-R as set forth in SEQ ID NO: 2"; "amino acid residues of 163-201 as the 67 group specificity" and Thr-181 - Asp 235 of SEQ ID NO: 2 as the stalk region specificity" and , does not reasonably provide enablement for any "natural ligand receptor of the TNF/NGF receptor family", "TBP-II" and "p75 TNF receptor" as well as any "67 group specificity" or "stalk region specificity" "function of the natural ligand receptor of the TNF/NGF receptor family.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The factors most relevant to this rejection are the scope of the claim, unpredictability in the art, the amount of experimentation required, and the amount of direction or guidance presented.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies "the natural ligand receptor of the TNF/NGF receptor family", "TBP-II" and "p75 TNF receptor" as well as 67 group specificity" or "stalk region specificity" other than those encompassed by "TNF-R as set forth in SEQ ID NO: 2"; "amino acid residues of 163-201 of SEQ ID NO: 2 as the 67 group specificity" (see page 4, lines 11-20) and Thr-181 - Asp 235 of SEQ ID NO: 2 as the stalk region specificity" (see page 5, lines 9-11)

While "the natural ligand receptor of the TNF/NGF receptor family", "TBP-II" and "p75 TNF receptor" as well as 67 group specificity" or "stalk region specificity" may have some notion of the structure or activity of these molecules or specificities, claiming biochemical molecules by certain names fails to distinctly claim what that molecule is and what it is made up of. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any "natural ligand receptor of the TNF/NGF receptor family", "TBP-II" and "p75 TNF receptor" as well as 67 group specificity" or "stalk region specificity".

For example, see Krakauer et al., in Paul (ed.) Fundamental Immunology Fourth Edition, Lippincott-Raven Publishers, Phildelphia, 1999, pages 775-784) for examples of the the breadth of the TNF/NGF family.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved, and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting a polypeptide structure from the disclosure of a limited sequence or a limited number of molecules (e.g. SEQ ID NO: 2; "amino acid residues of 163-201 as the 67 group specificity" disclosed on page 4, lines 11-20 of the specification and Thr-181 - Asp 235 of SEQ ID NO: 2 as the stalk region specificity" disclosed on page 5, lines 9-11 of the specification) and, in turn, utilizing predicted structural determinations to ascertain binding or functional aspects of the claimed antibodies and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation.

In re Fisher, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological and pharmacological activities.

A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance based on in vitro characterization assays to direct a person of skill in the art to select particular sequences as essential for in vivo characterization of their therapeutic potential (see disclosed/claimed utilities). A person of skill in the art could not predict which particular amino acid sequences of "natural ligand receptor of the TNF/NGF receptor family", "TBP-II" and "p75 TNF receptor" as well as any "67 group specificity" or "stalk region specificity" are essential and could be used in a therapeutic methods.

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) disclose that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Thus an assignment of function based upon sequence homology or identity without further functional analysis does not appear to provide sufficient enabling support for the claimed Toll homolog encoding nucleic acids and so the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

In further support for the lack of predictability in determining in structure and function Ngo et al. (in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.) disclose that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable. Therefore making and using the breadth of molecules in the claimed methods would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

With respect to the unpredictability of antibody binding and specificity, the following is noted.

For example, Lederman et al. (Molecular Immunology 28: 1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document).

For example, Li et al. (PNAS 77: 3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document).

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, making and using nucleic acids encoding the claimed "natural ligand receptor of the TNF/NGF receptor family", "TBP-II" and "p75 TNF receptor" as well as any "67 group specificity" or "stalk region specificity while providing or maintaining the claimed specificity and activity would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

With respect to the"function of the natural ligand receptor of the TNF/NGF receptor family"; it is noted that the "TNF/NGF receptor family comprises a myriad of distinct molecules and that each member of the family including the TNF receptor set forth in SEQ ID NO: 2 comprises pleiotropic and varying properties, as well known by the skilled artisan at the time the invention was made. Applicant has not enabled the inhibition of any or all of the functions of any natural ligand receptor of the TNF/NGF receptor family as well as TNF receptor set forth in SEQ ID NO: 2.TNF receptor set forth in SEQ ID NO: Applicant should limit the claimed methods to enabled methods of inhibition and should specifically recite the appropriate enabled endpoints enabled by the instant disclosure.

The specification does not adequately teach how to effectively achieve the inhibition of all endpoints including all therapeutic endpoints encompassed by the broad genus by administering antibodies to a particular TNF receptor. The specification does not teach how to extrapolate data obtained from in vitro binding inhibition assays to the inhibition of any function among a variety of functions among a myriad of TNF/NGF family members to lead to effective in vivo therapeutic methods, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the claimed antibody specificities exemplified in the specification to achieve the breadth of function inhibited, encompassed by the claims.

Given the relative incomplete understanding in the biotechnological field involved, and the lack of a reasonable correlation between the narrow disclosure in the specfication and the broad scope of protection sought in the claims, a rejection under 35 USC 112, first paragraph for lack of enablement is deemed appropriate.

In view of the lack of predictability of the art to which the invention pertains the lack of established therapeutic protocols for effective inhibition of the breadth of TNF/NGF functions encompassed by the claimed invention, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting any function of the broad genus of TNF/NGF receptor family by antibodies to a particular region(s) of the TNF receptor set forth in SEQ ID NO: 2.

Applicant should amend the claims to clearly recite the appropriate specificities and functions intended and enabled by the instant disclosure as filed to obviate this rejection.

9. Claim 16: It is apparent that the antibody 67 is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line CNCM I-1368 which produces this antibody. See 37 CFR 1.801-1.809.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

Given the disclosure (e.g. see column 15, paragraph 2) and the claims (e.g. see claims 3 and 16) encompassing the instant antibody 67 produced by the CNCM I-1368 cell line set forth in U.S. Patent No. 6,262,239; the conditions for the deposit of biological materials under 35 USC 112, first paragraph, with respect to antibody 67 have been satisfied.

10. Claims 12-16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 12-16 are indefinite in the recitation of "inhibiting the function of the natural ligand receptor of the TNF/NGF receptor of the TNF/NGF receptor family, comprising bringing into the vicinity of said ligand an antibody of the 67 group or the anti-stalk region" because the nature and metes and bounds of these "functions", "vicinity, "group" and "region" are ill-defined and ambiguous.

With respect to the broad genus of the TNF/NGF receptor family and the myriad of pleiotropic properties of members of said family; the nature and metes and bounds of the targeted functions inhibited by the claims are ambiguous and ill-defined.

Applicant is invited to amend the claims to recite "amino acid residues of 163-201 of SEQ ID NO: 2 as the 67 group specificity" (see page 4, lines 11-20) and Thr-181 - Asp 235 of SEQ ID NO: 2 as the stalk region specificity" (see page 5, lines 9-11).

It is not clear whether the "vicinity" refers to direct or indirect binding by the claimed antibody specificities . If the claims are encompassing indirect binding, then the term "vicinity" is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention

The recitation of "antibody of the 67 group" and "the anti-stalk region" in that they only describe the antibody specificities of interest by an arbitrary protein name. While the name itself may have some notion of the specificity of the claimed antibodies, there is nothing in the claims which distinctly claims the claimed and intended antibody specificities. Applicant should particularly point out and distinctly claim the "67" and "stalk region" antibody specificities by claiming sufficient characteristics associated with the protein (e.g. activity, molecular weight, amino acid composition, N-terminal sequence, etc.). Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that protein is and what the compositions are made up of.

B) Claims 13-16 are indefinite in that the recitation of "said extracellular domain" does not antecedent basis.

C) Claims 13-16 are indefinite in that the recitation of "said antibody is a peptide or antibody" is ambiguous and confusing in that the independent claim only recites antibody and that dependent claims recite an antibody as a genus as well as a subgenus.

D) Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

11. Given the prosecution of the antibody specificities in parent application USSN 08/476,862, now U.S. Patent No. 6,262,239 and an updated search; it appears the instant methods as they read on employing antibodies directed towards "amino acid residues of 163-201 as the 67 group specificity" and Thr-181 - Asp 235 of SEQ ID NO: 2 as the stalk region specificity" appear free of the prior art.

Again as pointed out above; applicant is invited to verify that the instant claims have written support and enablement under 35 USC 112, first paragraph, for the instant claims to priority U.S. and foreign applications. The instant claims may not have the benefit under 35 U.S.C. § 120 and § 119 of all of the priority filing dates. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph

Applicant is reminded that affidavits and declarations, such as those under 37 C.F.R. § 1.131 and 37 C.F.R. § 1.132, filed during prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit, the applicant should make the remarks of record in the later application and include a copy of the original affidavit filed in the parent application

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

PHILLIP GAMBEL

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
September 24, 2001